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Targeting Oxidative Stress to Restore Immune Balance: Phytochemical Interventions in Cancer and Chronic Inflammation

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ABSTRACT

Oxidative stress is both a driver and a consequence of dysregulated immunity across cancer and chronic inflammatory diseases. Reactive oxygen and nitrogen species (ROS/RNS) shape antigen presentation, cytokine networks, and cell death pathways; at pathological levels they derail tolerance, fuel fibrosis, and enable tumor immune evasion. This review synthesizes mechanistic links between redox biology and immune balance, spanning sentinel pathways (Nrf2/Keap1, NF-κB, STAT3, MAPKs, HIF-1α), immunometabolism (AMPK-mTOR, glycolysis–OXPHOS coupling), and microenvironmental cues (hypoxia, ferroptosis, lipid peroxidation). We evaluate phytochemical classes such as polyphenols, terpenoids, organosulfur compounds, alkaloids, and lignans as redox-active modulators capable of recalibrating innate and adaptive responses while sparing antimicrobial or anti-tumor effector functions. Emphasis is placed on how these agents impact dendritic cell fitness, macrophage polarization, T-cell exhaustion, myeloid-derived suppressor cells (MDSCs), and stromal crosstalk. We summarize formulation and pharmacokinetic advances (nanoformulations, phytosomes, inhaled/topical delivery), safety and drug–drug interaction considerations, and the translational evidence landscape. A pragmatic framework is proposed for endotype-guided deployment of phytochemical combinations alongside standard therapies to restore immune balance.

Keywords: oxidative stress; immunometabolism; Nrf2; NF-κB; phytochemicals; tumor microenvironment

INTRODUCTION

Persistent oxidative stress is a convergent hallmark of malignant progression and chronic inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis, metabolic dysfunction–associated steatohepatitis, and chronic obstructive pulmonary disease [1]. While low to moderate levels of reactive oxygen and nitrogen species act as indispensable second messengers for pathogen killing, antigen receptor signaling, and wound responses, sustained excess distorts danger sensing, resolution programs, and tissue repair [2]. In tumors, redox imbalance fuels genomic instability, pro-angiogenic signaling, epithelial–mesenchymal transition, immune suppression, and therapy resistance [3]. In sterile inflammation, it perpetuates parenchymal injury, fibroblast activation, and scarring. Phytochemicals such as bioactive plant-derived small molecules offer pleiotropic, network-level modulation of both redox and immune pathways [4]. Rather than behaving as simple radical sponges, many operate through transcriptional reprogramming, metabolic rewiring, and organelle quality control to restore homeostatic set points [5]. The translational aim is not wholesale oxidant removal, which can blunt essential defense functions, but deliberate retuning of redox tone to re-enable protective immunity, limit collateral damage, and promote controlled resolution.

Oxidative Stress and Immune Imbalance

Major ROS and RNS sources include NOX enzymes at membranes and phagosomes, mitochondria with altered electron transport, uncoupled nitric oxide synthase, xanthine oxidase, and myeloperoxidase in activated neutrophils [6]. Oxidized lipids such as 4-hydroxynonenal, reactive aldehydes, and advanced glycation end-products covalently modify proteins and nucleic acids, generating neoepitopes and impairing proteostasis [7]. Excess oxidants hinder dendritic cell cross-presentation, bias macrophages toward tissue-damaging phenotypes, drive neutrophil extracellular traps that intensify thrombosis and cytokine release, and stabilize immunosuppressive adenosine signaling under hypoxia [8]. In T cells, persistent oxidative pressure limits mitochondrial spare respiratory

capacity, promotes PD-1–associated exhaustion, and constrains memory formation [9]. In cancer, ROS cooperate with oncogenic signaling to stabilize HIF-1α, activate STAT3, and induce COX-2/PGE2, recruiting regulatory T cells and myeloid-derived suppressor cells while excluding cytotoxic lymphocytes [10]. In chronic inflammation, overlapping cues perpetuate NF-κB–driven cytokine loops featuring TNF-α, IL-1β, and IL-6, amplify ferroptotic and necroptotic damage, and lock tissues into a feed-forward cycle of remodeling and fibrosis [11].

Signal Integration: From Nrf2 to STAT3

The Nrf2/Keap1 axis coordinates antioxidant and detoxification programs, including glutathione synthesis, NADPH regeneration, and heme oxygenase-1, thereby protecting antigen-presenting cells and barrier epithelia and improving mitochondrial quality control [12]. However, indiscriminate or continuous activation risks blunting required antimicrobial or antitumor oxidants. NF-κB and MAPKs (p38, JNK, ERK) translate redox cues into context-specific cytokine programs, while STAT3 links oxidative stress to immunosuppression, angiogenesis, and metabolic reprogramming [13]. HIF-1α couples hypoxia and ROS to glycolytic shifts that can be protective during acute effector responses but pathological when sustained [14]. AMPK–mTOR integrates nutrient and redox status with autophagy, a key route to clear damaged mitochondria and limit inflammasome activation [15]. Collectively these nodes form a tunable network in which therapeutic benefit arises from adjusting pathway gain and timing rather than from binary inhibition.

Immunometabolism and Organelle Quality Control

Immune function depends on flexible fuel use. Effector T cells and classically activated macrophages favor aerobic glycolysis for rapid ATP and biosynthesis; memory T cells and regulatory macrophages rely more on fatty acid oxidation and intact mitochondria [16]. Oxidative stress collapses this flexibility, causing mitochondrial depolarization, excessive mitophagy or, paradoxically, defective mitophagy with DAMP release (mtDNA, cardiolipin) that intensifies inflammation [17]. Phytochemicals influencing AMPK activation, PGC-1α-mediated biogenesis, and mitophagy (e.g., curcumin, resveratrol, quercetin, berberine) can restore respiratory capacity, support memory T-cell formation, and reduce NLRP3 inflammasome fueling [18].

Tumor and Chronic Inflammation Microenvironments

The tumor microenvironment (TME) is hypoxic, acidic, lipid-peroxidized, and rich in suppressive myeloid cells. Elevated ROS in myeloid cells impairs T-cell receptor signaling via cysteine oxidation and nurtures MDSC differentiation [19]. Lipid peroxidation products foster ferroptosis sensitivity in tumor cells but also can kill infiltrating lymphocytes [20]. In chronic inflammatory tissues, ROS-driven stromal remodeling hardens extracellular matrix, stiffening mechanical cues that further activate fibroblasts and macrophages [21]. Effective redox modulation should therefore target both immune and stromal compartments and be compatible with radiotherapy, chemotherapy, targeted agents, and immunotherapies (checkpoint blockade, CAR-T) [22].

Phytochemical Classes and Mechanistic Actions

Polyphenols (flavonoids such as quercetin, EGCG, baicalein; phenolics such as curcumin, resveratrol) often activate Nrf2, inhibit NF-κB/STAT3, modulate MAPKs, and promote autophagy/mitophagy [23]. They improve dendritic cell antigen presentation, reduce MDSCs and Tregs in preclinical models, and can resensitize tumors to checkpoint blockade by lowering suppressive cytokines and adenosine signaling [24]. Terpenoids (ursolic/oleanolic acids, carnosol, carotenoids) stabilize membranes, modulate NOX/mitochondrial ROS, and influence macrophage polarization [26]. Organosulfur compounds (allicin, sulforaphane) exert thiol-reactive chemistry that reprograms both microbial and host redox tone, with sulforaphane a canonical Nrf2 inducer [25]. Alkaloids (berberine, piperlongumine) affect AMPK–mTOR and ROS thresholds differentially in tumor versus immune cells; piperlongumine can selectively raise tumor ROS past cytotoxic thresholds while sparing normal cells [26]. Lignans (silibinin) and coumarins add hepatoprotection and anti-fibrotic effects relevant to chronic inflammation [27].

Delivery, Pharmacokinetics, and Tissue Targeting

Many phytochemicals are poorly soluble, unstable, or rapidly conjugated. Nanoformulations (liposomes, solid lipid nanoparticles, polymeric micelles, nanoemulsions), phytosomes, and amorphous solid dispersions enhance bioavailability and enable co-delivery with standard drugs [28]. Ligand-decorated nanoparticles (mannose, folate) target dendritic cells or tumor-associated macrophages; redox- or pH-responsive carriers release cargo in inflamed or hypoxic niches. For cancers of the lung or skin and airway inflammatory diseases, inhaled or topical routes achieve high local exposure while reducing systemic burden [29]. Pharmacokinetic endpoints should include plasma, interstitial, and intracellular immune-cell concentrations; lesion penetration; and compatibility with food and concomitant medications.

Restoring Immune Balance: Practical Mechanisms

Tuning ROS/RNS without immunoparesis is central. The objective is to restore signaling-quality oxidants while curbing collateral damage. Timed, moderate Nrf2 activation can protect epithelium and dendritic cells, while preserving NOX/iNOS-dependent microbial or tumoricidal functions [31]. Autophagy enhancement clears damaged mitochondria and supports antigen processing. Inflammasome calibration, reducing maladaptive NLRP3

activation while retaining protective IL-1 family signaling prevents pyroptotic tissue loss [32]. Rebalancing immunometabolism via AMPK activation improves T-cell persistence and reduces pathological glycolysis in chronically inflamed tissues [33]. Collectively, these shifts move macrophages toward resolving phenotypes, refresh exhausted T cells, and reopen the window for effective adaptive immunity [34].

Safety and Drug–Drug Interactions

Phytochemicals can modulate CYPs (1A2, 2C9, 2C19, 2D6, 3A4), UGTs, and transporters (P-gp, BCRP), creating interaction potential with chemotherapeutics, targeted agents (TKIs), immunosuppressants, antiplatelets/anticoagulants, and anti-inflammatories [35]. Rifampicin-like inducers, azole inhibitors, or antiretrovirals may alter phytochemical exposure, and vice versa. Over-suppression of NF-κB or ROS risks impairing antitumor immunity; conversely, pro-oxidant phytochemicals combined with anthracyclines or radiotherapy could amplify off-target toxicity without careful dosing [36]. Quality control (standardized extracts, contaminant testing) and monitoring (liver enzymes, renal function, coagulation where relevant) are essential, particularly in frail or polypharmacy populations and during pregnancy.

Evidence Landscape

Preclinical studies consistently show improvements in oxidative markers, antigen presentation, macrophage polarization, and T-cell function, with tumor growth delay or reduced inflammatory scoring across models [37]. Combination strategies like phytochemical plus checkpoint inhibitor, chemotherapy, or anti-fibrotic often outperform monotherapy in animals. Early-phase human studies in chronic inflammation report biomarker improvements (reduced malondialdehyde, improved glutathione redox, lower CRP) and symptom benefits; cancer trials remain limited and heterogeneous, sometimes focusing on quality of life or chemotherapy tolerance (e.g., hepatoprotection, mucositis reduction) [37]. Standardization of preparations, validated pharmacokinetics, and biomarker-stratified, adequately powered trials are needed to determine effects on hard outcomes (response rate, progression-free survival, organ function preservation) [38].

Research Gaps and Future Directions

Key gaps include: defining dose–response windows that separate protective recalibration from immunosuppression; mapping cell-type specific redox setpoints in human tissues; resolving pharmacology in inflamed or hypoxic compartments; and establishing interactions with contemporary therapies (checkpoint inhibitors, CAR-T, JAK/BTK inhibitors, anti-fibrotics). Advanced delivery platforms, real-time redox imaging, and systems immunology should guide iterative trial design. Regulatory-grade standardization and comparative effectiveness against existing adjuncts will be critical for adoption.

CONCLUSIONS

Oxidative stress links oncogenesis and chronic inflammatory pathology through shared damage and signaling circuits. Phytochemicals properly characterized, formulated, and timed can retune these circuits, restoring immune balance without sacrificing necessary effector functions. The most promising path forward is no single agents but endotype-guided, combination regimens that integrate phytochemicals with established therapies, supported by rigorous pharmacology and biomarker-driven trials. With this strategy, redox-targeted phytochemical interventions could become practical tools to improve outcomes in cancer and chronic inflammation.

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